PIONEERING THE FUTURE

2014 Annual Report

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Institute for Systems Biology

Institute for Systems Biology

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THE TRANSFORMATIVE POWER OF PHILANTHROPY

This year's annual report features **Bill Bowes**, a San Francisco venture capitalist and philanthropist, and one of ISB's biggest supporters. Bill has been a valued colleague and a good friend for many years – we started Amgen and Applied Biosystems together in the 1980s. He's a true Renaissance man.

My colleagues and I are incredibly grateful for his extraordinary generosity to the Institute. His support has allowed us to hire new faculty which, along with his unwavering commitment for our pioneering approaches to research, is enabling us to lead the way in transforming medicine.

IT IS UNIQUE INDIVIDUALS LIKE BILL THAT PRESENT ISB WITH THE RESOURCES WE NEED TO **"INVENT THE FUTURE OF MEDICINE."**

OPTIMIZING WELLNESS AND MINIMIZING DISEASE

While the American healthcare system continues to focus almost entirely on diagnosing and treating disease instead of keeping people well, ISB continues to make great strides in disrupting that system. In fact, we are at the forefront of establishing an entirely new healthcare sector – scientific wellness.

As always, my colleagues across ISB have made notable discoveries to advance the study of cancers, post-traumatic stress, tuberculosis, malaria, rare diseases (e.g. Adams-Oliver syndrome and peroxisomal disorders), ocean acidification, and various aspects of the microbial genome. We share some research highlights from 2014 later in this report.

But 2014 was particularly exciting because we brought the 100K Wellness Project to life. This Framingham-like study for the digital age was launched with a 10-month pilot study of 107 well individuals through the Hundred Person Wellness Project. The goals of this pilot were to:

- Present actionable recommendations to the participants that could improve their health
- Potentially identify transitions from disease-to-wellness, and wellness-to-disease
- Document changes in health and wellness
- Create a framework for establishing early transition markers and scientifically validated metrics for wellness
- Develop a framework for scaling the project cost-effectively, including methodologies for real-world application

As discussed in detail in the Vision for the Future of Health Care section of this annual report, ISB made significant progress in each of these goals. We have also developed a pathway to scale the project from 100 to 100,000, with ISB focusing on its core scientific strengths and engaging with partners to recruit and directly engage with participants. Our first major partner is Arivale, the spin-out company that grew out of the pilot study. We believe that ISB and Arivale will together present the opportunity to transform the American healthcare system – moving it toward scientific wellness - and eventually bringing wellness potentially to all Americans, letting them optimize their human potential and avoid disease.

Lee Hood

Lee Hood, MD, PhD
President and Co-founder, Institute for Systems Biology

BILL BOWES: A QUIET FORCE FOR SOCIAL GOOD

By Gene Stout

When Bill Bowes and Dr. Lee Hood met in 1980, they began a business relationship and friendship that was sealed over a clunker of a machine hiding in a basement at Caltech. Hood had invented a device that automated protein sequencing that he believed would transform biology.

"IT WAS COMPLETELY UNMANUFACTURABLE," SAYS BOWES. "BUT IT WAS POTENTIALLY USEFUL."

Indeed, Hood had presented his prototype to 19 medical device companies and was rejected 19 times. But Bowes recognized Hood's "imaginative inventiveness" and agreed to invest $2 million to develop this sequencer.

"This was a machine that really took a lot of ingenious thinking to come up with," Bowes says. "Lee had a this-is-going-to-change-the-world kind of attitude and he was a good salesman (full of) rambunctiousness."

Bowes, who received a BA in economics from Stanford University and an MBA from Harvard Business School, began his career as an investment banker in the 1950s. In 1980, he launched U.S. Venture Partners and then shifted his efforts to philanthropy in 1992 with the founding of the William K. Bowes Jr. Foundation. The Foundation boasts more than $400 million in assets and grants nearly $40 million per year to nonprofits focused on medical research (stem cells and cancers), college access, arts, and higher education.

While Bowes focuses most of his philanthropy on causes based in his native San Francisco (such as the Exploratorium – a sprawling educational facility with 500 interactive science exhibits that Bowes suggests the wearing of "track shoes" is necessary to explore), he has contributed a total of $18 million to Institute for Systems Biology during his tenure of more than a decade on ISB's board of directors. ISB is one of the top beneficiaries of the William K. Bowes Jr. Foundation.

"BILL IS REALLY INTERESTED IN FIRST-CLASS SCIENCE," SAYS HOOD, WHO CO-FOUNDED ISB IN 2000 AND SERVES AS ITS PRESIDENT. "BUT HE HAS MANY TALENTS AND GREAT DIMENSIONALITY, WITH BROAD INTEREST IN THE ARTS, MUSIC AND CIVICS. HE'S REALLY AN EXCEPTIONAL PERSON."

Bowes, now in his late 80s, is a kindly and soft-spoken World War II veteran who followed his instinct to champion biomedical research, education and social good. He made shrewd investments in biotechnology and high tech companies, notably Amgen, Applied Biosystems and Sun Microsystems, which helped him accumulate a fortune that he is now leveraging to make long-lasting improvements in society and the lives of others.

In an interview at his foundation headquarters at One Maritime Plaza in San Francisco, Bowes shared his story and why he's been such an ardent supporter of ISB.

Q: AS A MEMBER OF THE BOARD OF DIRECTORS OF ISB, WHAT GOALS DO YOU SUPPORT FOR THE ORGANIZATION?

BOWES: TO CHANGE THE WAY MEDICINE IS DONE. CHEAPER AND BETTER. SIMPLE AS THAT.

Q: What inspired you to become a venture capitalist?

Bowes: One of the real pioneers of venture capital was a guy named Georges Doriot, who was in Boston and taught a class at Harvard Business School. It was a very popular and inspiring class. I guess that kind of got me started, even though I didn't go into venture capital for another few decades. But when I started investment banking, venture capital didn't really exist.

Q: What motivates you as a venture capitalist and philanthropist with a passion for scientific advancement?

Bowes: I guess medical research. I support individual scientists who are young and terrific and they're in those particular years when money's hard to come by. They're not eligible for grants yet. So that's where I come in at various institutions.

Q: How did you meet Dr. Hood?

Bowes: I had made an informal but pretty intensive survey of southern California scientists. We were going to place Amgen in southern California because of the excellence of the science there that had not yet been spoken for by a company. And after getting to know Lee Hood at Caltech, I learned that he had a machine down in the basement which was useful.

Q: The protein sequencer?

Bowes: Yes. So I went over to see him. He was in his office and wearing Lederhosen, which appealed to me. And his machine looked really good. Completely unmanufacturable. Sort of a clunker. But potentially useful. What took a lot of time was to get the intellectual property problems resolved with Caltech. They were business-unfriendly in those days. But they finally said, 'OK.' We sort of wore them down.

Q: What was the next step in the development of the protein sequencer?

Bowes: We found a guy at Hewlett-Packard, Sam Eletr, and his job was to take products like Lee Hood's that had been tossed over the wall, and he would product-tize them. That was his job. He was a brilliant engineer.

Q: This led to the launch of Applied Biosystems?

Bowes: Yes. We moved the company up here to the Bay Area. And put Sam in charge of it. And we financed the company by getting big companies to put in deposits for early machines, which was very non-dilutive financing. We had venture capital in there too, of course. The company just did extremely well. And after a number of years, it was bought by another big company, Life Technologies.

Lee Hood with his protein sequencer at Caltech in the 1980s.

Q: You have a knack for recruiting and hiring people to run new companies, such as George Rathmann at Amgen. What did you see in his leadership abilities at the time you were launching the company?

Bowes: George was a proven leader. He had a big job at 3M, and he had a big job at Abbott Laboratories. He ran diagnostics. He got interested in the new biology and he took a sabbatical from Abbott and spent a year at UCLA in a lab there. So he was the perfect guy. He had executive experience, and he was interested in the new biology. And he was willing to leave a lush life on the North Shore of Chicago and come live in Ventura, Calif., and start with three other people from scratch. Dead scratch. That's the kind of guy you want.

Q: You also serve on the boards of the Asian Art Museum, Grace Cathedral and the Hoover Institution at Stanford. And you're also a jazz fan. Is there an entity here in San Francisco that you support?

Bowes: SF Jazz. Just last year they finished their new building. They've been in venues all over the city, and now they have their own place. The only other one in the country like it is in New York.

Q: What role did you have in the construction of that building?

Bowes: I was a contributor. I was on the campaign committee, and I did some individual investing. I helped choose the architect and so forth. I'm really proud of how it turned out. It's probably got the best sound in San Francisco.

Q: Did your interest in jazz begin in the '40s?

Bowes: Yeah

Q: Anyone in particular?

Institute for Systems Biology

Bowes: Louis. Louis Armstrong. He used to come to town with his gang twice a year. I never missed it. I love the way he played the trumpet. And he could sing a little too. Or growl.

And Jack Teagarden. He was local. And Earl

"Fatha" Hines. The whole gamut.

Q: Were there other people in American culture and society that you admired? Musicians, artists, scholars?

Bowes: Maybe Mike (John Michael) Bishop, who was a Nobel Laureate at UCSF. And Stan Prusiner, same thing. And I'm a great admirer of John Hennessey, the president of Stanford University. There's a real long list, I guess.

Q: You're a member of the executive committee of the San Francisco Conservatory of Music. What are their objectives?

Bowes: It's an absolutely first-class conservatory. The plan now is to have student living quarters right there because it's been a big competitive disadvantage for them compared to other schools where the students can live in a nice apartment right on the grounds. Their students are scattered around the city. So we bought two buildings, and we're going to transform them into student housing. We think that's going to make a huge difference in the quality of students we attract. Everyone wants to come to San Francisco, but not everyone wants to scramble for housing.

Q: What do you do for the Environmental Defense Fund?

Bowes: What I like about EDF is that you can invest in individual projects there and not throw money into the pot. So I have some individual initiatives inside EDF that suit me better than just putting money in.

Q: What for example?

Bowes: Bringing back the fisheries of the world. We started in Alaska with halibut. The halibut were getting less and less populous in the sea, and all the authorities could think of was to shorten the season. So they got down to three weeks in a season and mayhem on the water as everyone was trying to get their fish all at one time. And the fish were rapidly piling up on the docks and becoming unsalable.

Q: What was your solution?

Bowes: And so we instituted a program that was experimental at first. A program called "catch share," which determined scientifically how much fish a body of water could sustainably produce and then divide it among the local fishermen to get their share of the catch. They can do it any time of the year they want, and that's what they have, no more and no less. They find that their share increased over the years as the fish population increased. And they're finding that their fish are more valuable because they're not being caught all at once, they're being caught through the year. And they get down to the market in prime shape.

Q: How did your childhood shape you? Your father was a businessman and your mother a physician. What did you learn from them that was helpful later on?

Bowes: Nothing specific. But it was a very nice combination of parents to be brought up around.

Q: Your mother was one of the first two women to graduate from Stanford School of Medicine. Was she also an exceptional parent?

Bowes: She was a fantastic person. I was impressed that she went back to teaching at Stanford Medical School when the war broke out. She did that for two or three years. It was hard work. But it kept her on her toes.

Gene Stout has a unique perspective on this region's cultural landscape, having written about music, autos, travel, wine and restaurants for more than three decades. He is active as a writer, editor, blogger and regular contributor to The Seattle Times and other publications. His stories have appeared nationally through the New York Times and Hearst Corporation news services.

A VISION OF THE FUTURE OF HEALTHCARE

Lee Hood, MD, PhD, President
Nathan Price, PhD, Associate Director
Sui Huang, MD, PhD, Professor

In this article we provide the background and a concise summary of the pathway the Institute for Systems Biology (ISB) followed to execute the Hundred Person Wellness Project – a longitudinal, pilot study on 107 well individuals in 2014 that created a dense and dynamical data cloud of billions of data points for each participant.

During the short duration of this pilot study, many of the participants made life-altering changes to improve their health and wellbeing, and ISB made some profound discoveries. In fact, what ISB learned far exceeded its expectations.

This pilot study was strikingly successful in:

- Uncovering the potential for optimizing individual wellness.
- Driving forward new scientific discoveries.
- Creating unique new partnership and other opportunities for ISB.

In the grander scheme, this is one key to the transformation of contemporary healthcare in that the adoption of scientific wellness throughout the system over time – will eventually create a medicine that is predictive, preventive, personalized and participatory (P4 medicine).

INTRODUCTION

Today, we spend more than 17% of the US GDP on healthcare – far more than any other country – and yet by many measures we are ranked near the bottom of the top 20 developed countries of the world in the quality of our healthcare. Over the past 15 years, ISB has pioneered a series of systems-driven (global) advances that have defined systems medicine (a systems or global approach to disease) and have begun to delineate P4 medicine. Indeed, over the past few years there has been a convergence of four major scientific and social thrusts to more completely define P4 medicine: systems medicine, big data/analytics, digital quantified-self measurements, and consumer/patient-activated social networks.

P4 MEDICINE

P4 medicine differs from contemporary medical practice in numerous ways:

- It is proactive rather than reactive, addressing underlying issues that affect health before symptoms arise.
- It focuses on parameters specific to individuals rather than relying on averages based on unstratified populations of patients.
- It focuses on the importance of addressing wellness and disease rather than primarily disease.
- It generates dense (billions of data points) and dynamical (repeated measurements over time) individual data clouds (high-dimensional "big" data, i.e., genomes, proteomes, metabolomes, gut microbiomes, clinical chemistry and quantified-self measurements). These dense and dynamical data clouds capture the key elements of health: genetics and environment.
- These data can be integrated to identify the biological networks that govern development, physiology and aging. Determining how these networks are altered in diseases and how these "disease-perturbed networks" differ from their normal counterparts allow fundamental insights into disease mechanisms. Further, it becomes possible to design new strategies for identifying disease biomarkers and delineating leverage points for intervention, such as drug targets.
- For clinical trials, P4 medicine highlights the importance of gathering large numbers of individuals with dense and dynamical data clouds for each participant and then segregating them according to the traits of interest (e.g., response to a drug, or adverse reactions to a drug). This view also showcases the importance of "N-of-one" (N=1) studies of clinical processes to gain deep insights into wellness or disease.
- Importantly, whole genome sequencing coupled with these longitudinal data sets allows us to make predictions contextualized for each individual in order to specifically interpret dynamic measurements and networks that vary between individuals. Contemporary medicine uses large cohorts of individuals and treats them as uniform – even though each individual is genetically and environmentally unique. This averaging over highly heterogeneous populations obscures information on the individual that is relevant for personalized medicine and suffers from the problem of low signal-to-noise ratio, as exemplified by the failure of randomized clinical drug trials to predict drug effects on specific, individual patients.
- Online social networks are important for educating patients (and physicians), about this emerging P4 medicine. They also help build community and create relationship-based accountability, which increases motivation for long-term lifestyle change. Crowdsourcing provides individuals the opportunity to discover and share new ways to improve their own health through aggregated – but not averaged, knowledge. It also provides individuals with a means to persuade their own physicians (sometimes conservative or reluctant) to embrace and understand the new concept of scientific wellness and the power of P4 medicine – and it creates change agents in the often rigid current system.

> **"Most came to realize that genetics do not determine their destiny..."**

SCIENTIFIC WELLNESS: A NEW INDUSTRY AND AN UNTAPPED MARKET

P4 medicine has two central thrusts – improving wellness and helping to avoid disease. Perhaps 97% of society's healthcare resources are spent on disease and very few on wellness. Accordingly, wellness – and how to enhance it and extend it – has not been studied very thoroughly by scientists. ISB proposes to change this by taking a systems – approach to understanding wellness – and thereby make it scientific. For example, we will establish quantitative metrics that will allow us to evaluate both the physiological and psychological aspects of wellness.

Scientific wellness will emerge as a new sector in healthcare. Our prediction is that within a 10-15 year period the wellness industry will promote such a dramatic shift in healthcare dollars from the disease to the wellness sectors that the scientific wellness industry will exceed the "disease" industry in market cap. ISB, being at the source of the first dense and dynamical data clouds, is well positioned to catalyze companies that will populate this new arena of scientific wellness – and perhaps even create the Google of this emerging industry.

BRINGING P4 MEDICINE TO THE HEALTHCARE SYSTEM

A critical question has always been how to bring P4 medicine to the healthcare system. In ISB's 2012 annual report, one of us (LH) first suggested a longitudinal Framingham-like study for the digital age that would include 100,000 well individuals and would delineate a dense and dynamical data cloud for every participant.

In 2014, Lee Hood and Nathan Price and other ISB colleagues initiated the Hundred Person Wellness Project – a 10-month pilot study with 107 individuals. This project has been extremely valuable for both the participants – and the study team for the deep science we have learned.

The Hundred Person Wellness Project is the first real-world test of Hood's P4 medicine paradigm – that is, using a systems approach to ultimately transform healthcare. The pilot study focused on optimizing wellness through longitudinal data collection from whole-genome sequencing, clinical laboratory tests (3x), gut microbiome (3x), and quantified-self measurements (diet, exercise, sleep, etc.) from each individual.

These dense and dynamical individual data clouds have revealed multiple "actionable possibilities" for each participant -- that if acted upon either improved their wellness or helped them to prevent a disease. Each of the participants was aided in interpreting their data by a wellness coach who played a critical role in bringing the actionable possibilities to the individuals' attention and in guiding them on how to change their behaviors by acting on the actionable possibilities.

At the individual level, participants had an opportunity to get a snapshot of what it truly means to begin to optimize their health and hopefully avoid disease. Most of them established a new and very personalized baseline for their own health and 70% of them acted on the coaching recommendations provided. Continued measurements also allowed participants to observe firsthand the responses to their behavior changes, which further motivated them over the course of the study. They also realized that new actionable possibilities will emerge over time with changes to their individual environment and lifestyle.

These data have opened up exciting new opportunities for examining the dark matter of human biology and disease, areas that no one has ever traversed before by creating more than 35,000 fascinating data correlations. Strikingly powerful analytical tools have been developed in the course of analyzing this first-of-its-kind data set. This effort has resulted in a rich database of results, which is poised to expand dramatically in the years ahead.

When ISB launched this study in 2014, it hoped to develop a series of stories about how actionable opportunities have changed the wellness of the participants – or made them aware of how they can avoid disease in the future. The pilot study results greatly exceeded ISB's expectations and below are a few examples from the participants:

- One participant that was homozygous (inherits one bad copy of a gene from each parent) for a gene that can cause hereditary hemochromatosis, a condition of excess iron absorption. He also had very high iron biomarkers from the first blood draw lab results, showing that the disease he was at genetic risk for had manifested itself. The individual was referred to his physician and was diagnosed with hemochromatosis and treatment was initiated. If untreated, hemochromatosis leads to joint degeneration, liver fibrosis, heart failure and diabetes – and chronic disease. With proper treatment, which this individual received, all of this can be avoided.
- Forty-three participants entered the study meeting diagnostic criteria for pre-diabetes. By the end of the study, seven individuals had completely normalized blood sugar and many others had favorable improvements in their pre-diabetes markers.
- Another individual had been working with her physician because of unexplained high levels of inflammation. The Study Team discovered that the individual had an abnormal microbe in her gut microbiome and so was started on prebiotic and probiotic supplements. After three months the inflammatory markers in the blood had normalized.

Scientific wellness will emerge as a new sector in healthcare. Our prediction is that within a 10-15 year period the wellness industry will promote such a dramatic shift in healthcare dollars from the disease to the wellness sectors that the scientific wellness industry will exceed the "disease" industry in market cap. ISB, being at the source of the first dense and dynamical data clouds, is well positioned to catalyze companies that will populate this new arena of scientific wellness – and perhaps even create the Google of this emerging industry.

- A number of the 107 participants viewed this study as the experience of a lifetime.
- Many realized that given the proper information, they could make decisions for themselves to improve their health in ways they didn't previously appreciate. Over time, this can have enormous effects on reducing risk for downstream debilitating and expensive chronic and other diseases. This is central to reducing the cost of healthcare.
- Most came to realize that genetics do not determine their destiny, but rather their potential for wellness or disease. With appropriate changes in behavior and lifestyle, one can circumvent many genetic limitations.
- Almost all individuals came to the study with the view that they were (for the most part) well. However, the study exposed for all individuals multiple actionable possibilities that could be acted upon to improve their wellness. This illustrated that most of us have unrealized potential for optimizing our wellness. Ongoing access to data measuring our individual state of wellness is critical for taking advantage of this potential. The fact that we will continue to discover new actionable possibilities as we integrate more data from such studies suggests that scientific wellness will be a lifelong journey of wellness opportunities.
- All individuals were convinced that the coach played a key role in achieving a 70% compliance to actionable possibilities – a remarkable accomplishment.
- Finally, most individuals wanted to go on to the next stage of the study.

ISB is moving forward with this study in two distinct directions.

Because of the remarkable advances in scientific wellness and ISB's unique role in this nascent area, we are strategically positioned to catalyze the adoption of P4 medicine by the US healthcare system. In fact, we are seeking out clinical and academic partners that will enable the many different possibilities outlined in this document – and are exploring a number of exciting opportunities in this arena.

STRATEGIC PARTNERSHIPS

We are seeking out strategic partners, both national and international, both industry and academia, to identify relevant populations of individuals to interrogate for wellness or in which the transition from wellness to disease (or the inverse) can be identified in real-time. This is why expanding disease monitoring to encompass the wellness time period is critical. Such longitudinal data at the individual level allows for the new dimension of dynamics in the dense data clouds. Examples of partnerships that we are exploring include the following:

- **A scientific wellness study of individuals from the Aboriginal tribes of Australia is being organized.** This will demonstrate that scientific wellness studies can be carried out for the poor as well as the rich or the middle class.
- **A study of individuals that have gone through the difficult treatment of breast cancer.** This will demonstrate the power of scientific wellness to transform the post-treatment lives of cancer patients.
- **A study of middle class Indians (country) that is focused on wellness in conjunction with diabetes.** This is an important study as diabetes is a disease that we know how to address and it would tackle a major healthcare issue for India (and most other developed, as well as developing countries) with the power of scientific wellness.
- **A scientific wellness study of 100-200 individuals with new types of assays with powerful new microfluidic approaches that measure complex phenotypes, epigenetics, and many immunological parameters.** This parallels efforts at ISB to miniaturize, automate, integrate and parallelize relevant wellness assays. Efforts like these are leading to the digitization of medicine – with potential impact like that of the digitization of communication (smart phones) that greatly reduce the costs, while opening up previously unfathomable new forms of services. Digitization of medicine is critical to strikingly reduce the cost of healthcare – democratizing scientific wellness to benefit the poor as well the rich.
- **International partnerships to extend P4 medicine.** ISB is also exploring the possibility of bringing scientific wellness to the healthcare systems of several countries, moving beyond the US to catalyze impact around the world.
- **Transforming medical education and bringing it into the 21st century**. ISB is currently exploring this opportunity with a number of existing medical schools, although it would be ideal to launch this with a new medical school to avoid the conservative constraints of the past.

> **"Scientific Wellness will emerge as a new sector in healthcare."**

For example, we could enroll a freshman class of medical students in a program similar to the Hundred Person Wellness Project for all four years of their education. Each year, we would design courses of increasing sophistication to enable them to learn about systems medicine, emerging technologies, systems-driven strategies and P4 medicine. This would recast classical medical school topics as they would be viewed through the lens of system thinking, combined with the integration and analysis of their own data. Four authors at ISB are just finishing a textbook on systems biology and systems medicine that could be instrumental in initiating this effort.

ARIVALE – A SCIENTIFIC WELLNESS COMPANY

We launched a scientific wellness company, Arivale, directed at bringing scientific wellness to the consumer in a way that will emulate the strategy of the Hundred Person Wellness Project described above. This is an attractive opportunity because it will permit us to generate 5,000 - 10,000 dense and dynamical data clouds in the next 18 months – optimizing wellness and minimizing disease for 100 times more individuals than in the Hundred Person Wellness Project.

This provides a scalable model to ultimately bring scientific wellness to vast numbers of individuals. With data from these individuals we can drive the scientific discoveries forward to move this field ahead and provide individuals with vastly expanded actionable possibilities to enhance their wellness and minimize their risk for disease.

ISB has an agreement with Arivale to analyze all of these data for consenting participants – opening up new opportunities for understanding human wellness and disease transitions, as well as exploring the dark matter of human biology and disease. The Arivale data will create possibilities for exciting new industrial strategic partnerships.

OUR VISION FOR THE FUTURE OF HEALTHCARE

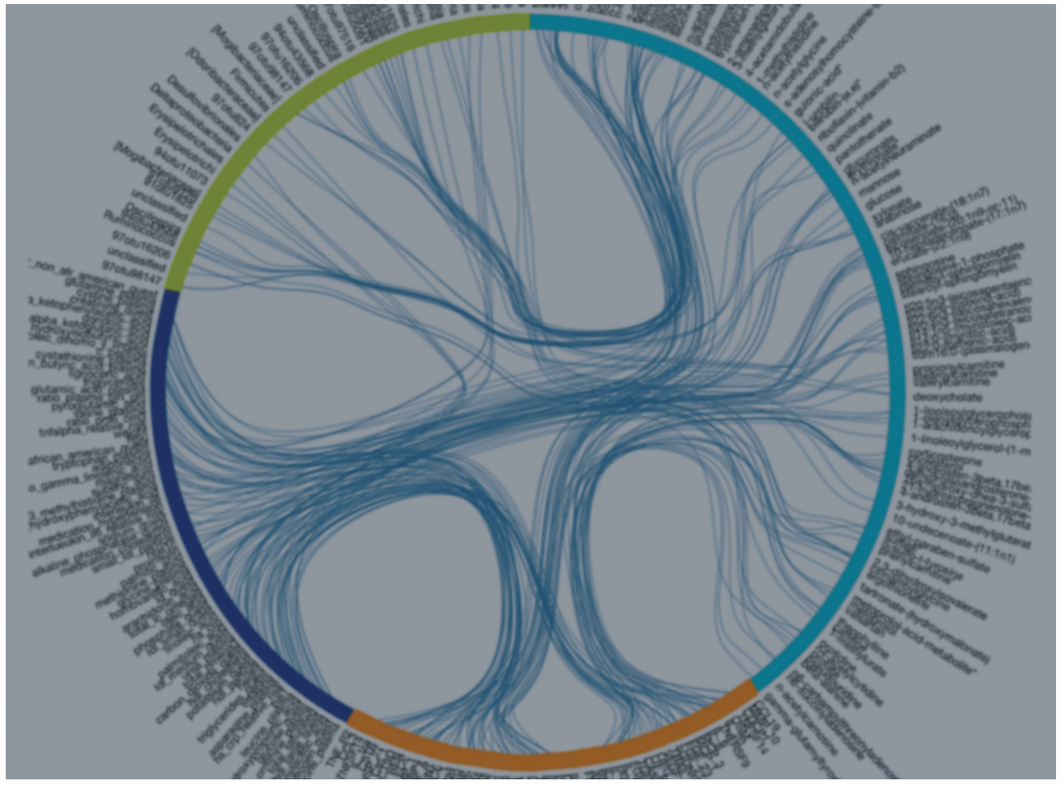
- P4 medicine will play a central role in healthcare of the future and in increasing wellness. Medicine will truly achieve the 4 Ps (participatory, the 4th P – means that the individual is at the center of his / her own healthcare).
- The health and disease states are assessed by evaluating both the genetics and the environments of each individual. Analyzing the dense and dynamical data clouds provides a powerful approach to assessing these two components and identifying actionable possibilities.
- Scientific wellness plays two important roles:
  - » It maximizes human potential by optimizing both physiological and psychological possibilities.
  - » With sufficient numbers of participating individuals, the data clouds allow us to define the signatures of wellness-to-disease transitions for all of the major diseases. We can then identify the earliest signs of an impending disease transition and use systems approaches to delineate the disease-perturbed networks – and thus develop the diagnostic and therapeutic reagents necessary to reverse the disease at the earliest possible stage. Such preemptive action across the spectrum of diseases will save the healthcare system billions of dollars.
- The scientific wellness industry will open tremendous opportunities for innovation and company creation. This will be a major driving force for the creation of cheaper and better assays that will lead to the digitalization of medicine. This will drastically reduce its cost – to the point where the rich as well as the poor can be served. This, in turn, will lead to a democratization of healthcare unimaginable even a few years ago.
- Tens of thousands of dense and dynamical data clouds will provide the information necessary to fundamentally change how pharmaceutical, biotechnology, nutrition and diagnostic companies practice their science. Longitudinal dynamical studies on tens of thousands of individuals from genetically stratified populations will transform how we understand early disease mechanisms, identify novel panels of biomarkers and drug candidates and come to understand nutrition in an increasingly sophisticated manner.

In the context of these observations, suppose that we could elevate normal individuals to the status of the wellderly by having them participate in a scientific wellness study and respond to all of their emerging actionable possibilities throughout their entire lives. If so, one could lead a mentally and physically active life far into the 90s. If scientific wellness can bring you to 100 as an effectively functioning individual, when you die it will most likely happen very quickly. This also suggests that scientific wellness must be a lifelong journey.

LOOKING AHEAD

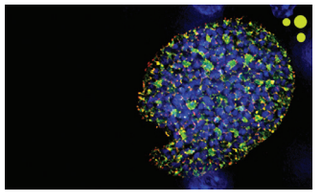
This is a unique time in the history of ISB. We need to go forward boldly to "invent the future" of healthcare. In E. O. Wilson's terms we are witnessing for healthcare a "consilience" or grand unification of science, the social sciences and the humanities – that extends far beyond the conventional cross-disciplinary nature of systems approaches to science itself, which ISB has pioneered.

Together, systems medicine, P4 medicine and the opportunities that have been created as a result of the Hundred Person Wellness Project will lead the way for a transformation of US and international healthcare.



Headlines 2014

MORITZ LAB



Jan. 9:

The Bug Stops Here: Arresting Malaria Parasites in the Liver Gives Immunity

ISB researchers collaborated with Seattle BioMed researchers to identify molecular building blocks required by malaria parasites to build cell membranes. Deleting key genes necessary for building cell membranes created a parasite that does not make the host sick and can't be passed on through the blood. Treating mice with modified parasites gave them complete immunity against malaria.

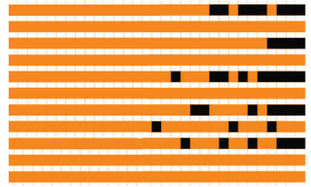
BALIGA LAB

Jan. 10:

ISB Study Shows: Domesticated Microbes Don't Forget Their Wild Roots

ISB researchers discover that microbes retain complex survival traits despite having been domesticated for more than 50 years. The study revealed that gene networks store a historic record of environmental change. The research reinforces the concept that model organisms can serve as authentic systems to study evolution of complex traits.

PRICE LAB



Jan. 12:

New ISB Software Makes It Easier to Curate and Analyze Microbial Genomes

Price Lab researchers worked with collaborators at the University of Illinois to create an easy-to-use software toolkit for comparing microbial genomes. Tools can be used to find orthologs, correct missing/inaccurate gene annotations, analyze gene gain and loss patterns, and build draft metabolic networks from reference networks. New ISB software offers predictive and analysis capabilities in a flexible way, making it easy to build customized analysis pipelines.

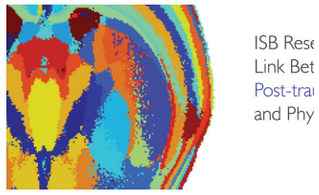
Headlines 2014
Continued

HOOD LAB

Feb. 11:
Dr. Lee Hood's Vision for Wellness Featured in Nature News

The journal Nature pubished a news article about Dr. Lee Hood's vision for the 100K Wellness Project and the March launch of the 100-person "Pioneers" study that eventually will scale to 100,000 individuals.

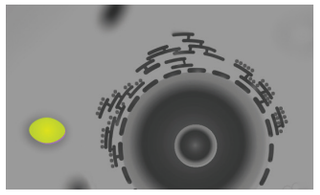
HOOD LAB



Feb. 19:
ISB Study Finds Molecular Link Between Simulated PTSD & Physical Heart Damage

Previous links between posttraumatic stress disorder (PTSD) and cardiovascular disorders were mostly thought to be psychological. Using mouse models, researchers at ISB and U.S. Army Center for Environmental Health Research found physical injury of heart tissue as a result of exposure to stressful environments. This research is important for developing future methods for early and objective diagnosis, and new therapeutic approaches for patients with PTSD and PTSD-associated ailments.

AITCHISON LAB



Feb. 19:
Tiniest Malfunctions in a Cell Can Cause Devastating Diseases

ISB researchers are studying peroxisomes, which are cellular organelles that are linked to a rare syndrome that causes progressive organ complications and infant mortality. Peroxisomes have a role in metabolizing and breaking down cellular waste. Because peroxisomes easily change shape and function according to a cell's needs, a systems approach is necessary to help decipher that complexity.

Headlines 2014
Continued

BALIGA LAB

Feb. 26:
ISB Researchers Discover Novel 'Switch' in Halobacterium salinarium That Turns Off Genes

ISB researchers discover a novel mechanism used by cells to rapidly turn "on" or "off" genes in order to change survival strategies in response to environmental events. The "switch" was discovered in Halobacterium salinarium and found to be conserved in diverse life forms. Research shows that microbes may use specialized switches depending on the type of environmental challenge they encounter.

HOOD & PRICE LABS

Feb. 26:
Science Translational Medicine Publication: 'Demystifying Disease, Democratizing Healthcare'

In the Feb. 26, 2014, issue of Science Translational Medicine, Dr. Lee Hood and Dr. Nathan Price, of Institute for Systems Biology, deliver an editorial stating the vision of the 100K Wellness Project. "Unsustainable cost increases threaten the global health care system, and further progress is stymied more by societal than technological factors. Only by engaging healthcare consumers (that is, patients) as pioneers who provide both health-related data and insights into pathophysiology can we meet these societal challenges and thus accelerate the pace of biomedical innovation."

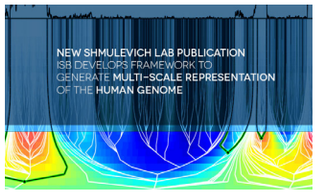
HOOD LAB

March 14:
Dr. Lee Hood Receives Geoffrey Beene Builders of Science Award from Research!America

Dr. Lee Hood received the Geoffrey Beene Builders of Science Award from Research!America at a ceremony on March 12, 2014, in Washington D.C., for his work pioneering the development of instruments that paved the way for the successful mapping of the human genome.

Headlines 2014
Continued

SHMULEVICH LAB



April 13:
Now Researchers Can Explore Genomic Data Across Space and Time

Understanding systems from a multiscale perspective gives us a more detailed and holistic view of how features or functions from each scale connect and interact in a given system. The challenge is integrating the different types of information that come from each scale in an efficient way that yields the most insight. ISB developed a new tool to make it easier for researchers to to integrate, analyze and visualize human genome data at multiple resolutions.

HOOD & PRICE LABS

May 15:
100K Wellness Project Article By Lee Hood and Nathan Price in Clinical Omics

Dr. Lee Hood, president of Institute for Systems Biology (ISB), and Dr. Nathan Price, ISB's associate director, publish an article about the 100K Wellness Project.

"We believe that a longitudinal, Framingham-like study of 100,000 well individuals and their dynamical data coulds could transform medicine."

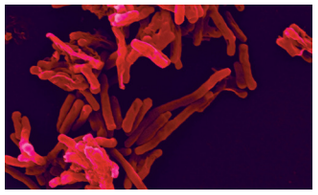
LOGAN CENTER

June 2:
Shifting the Education Paradigm: Hosting Community College Faculty for Systems Biology Workshop

Modern biology requires new educational strategies and approaches to engage and prepare students in this evolving discipline. ISB's Logan Center for Education has had a long history of impacting K-12 science education and is now making strides at the college level.

Headlines 2014
Continued

MORITZ LAB



June 20:
ISB Researchers Identify New Protein Modification Critical to TB Pathogen Growth

ISB and Seattle BioMed researchers collaborated and discovered a new protein post-translational modification in the human pathogen Mycobacterium tuberculosis (Mtb). Post-translational modifications are essential mechanisms used by cells to diversify protein functions and ISB scientists identified the rare phosphorylated tyrosine post-translational modification on Mtb proteins using mass spectrometry. Inhibiting phosphotyrosine modified amino acids in Mtb severely limits the growth of this widespread deadly pathogen.

BALIGA LAB

July 15:
Decoding the Microbial Gene-Recycling Program: Researchers 'Unzip' Genetic Instruction Manuals

Microbes are efficient because their streamlined genomes allow them to evolve and adapt rapidly to complex environmental changes. Decoding the highly-compressed information within a microbial genome requires sophisticated systems biology tools to map the genetic programs, and understand how they are executed. ISB researchers invented novel algorithms to unzip and decode microbial genomes into the EGRIN 2.0, an open-access multiscale model that captures instructions for executing the dynamic molecular processes in unprecedented detail.

SHMULEVICH LAB

July 23:
ISB Researchers Identify Four New Subtypes of Gastric Cancer That May Lead to New Targeted Treatments

Gastric cancer has a high mortality rate, but current classification systems haven't been effective in helping to identify subtypes relevant for treatment of the disease. TCGA (The Cancer Genomics Atlas) researchers have integrated molecular data from 295 stomach tumors and have discovered four subtypes of gastric cancer. Stratification of patients into these four subtypes paves the way for the development of new personalized therapies.

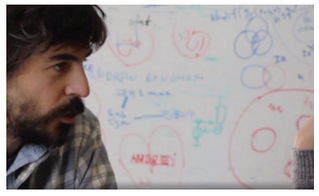
Headlines 2014
Continued

AITCHISON LAB

Aug. 1:
ISB is Co-Recipient of $10.9 Million NIH Grant for the National Center for Dynamic Interactome Research

The NIH's National Institute of General Medical Sciences has issued a Biotechnology Resource Grant of $10.9 million over five years to the National Center for Dynamic Interactome Research (ncdir.org) project. This project is a collaboration among The Rockefeller University, Institute for Systems Biology, Seattle BioMed, University of California at San Francisco, New York University and New York Structural Biology Center.

SHMULEVICH LAB



Aug. 15:
New Software Platform, Biocellion, Models Biological Systems at Unprecedented Scales

Computer simulation is a promising way to model multicellular biological systems to help understand complexity underlying health and disease. Biocellion is a high-performance computing (HPC) framework that enables the simulation of billions of cells across multiple scales. Biocellion facilitates researchers without HPC expertise to easily build and simulate large models.

RANISH LAB

Aug. 18:
New Structural Map Helps to Understand Aggressive Tumors

Aggressive tumor growth is linked to high activity of a macromolecular assembly called RNA polymerase I. ISB and FHCRC researchers collaborate to map the architecture of the assembly using a powerful crosslinking-mass spectrometry (CXMS) technology. Structural maps provide important insights into therapeutic targets for cancer treatment.

Headlines 2014
Continued

HOOD LAB

Aug. 25:
Analyzing Family Genomics Reveals New Culprit in Rare Disease Adams-Oliver Syndrome

Adams-Oliver syndrome (AOS) is a rare congenital disease characterized by scalp lesions and limb defects. Additional vascular abnormalities and heart defects can lead to early death in some patients. By analyzing twelve families affected with the disease, we identified causal mutations in a new disease gene, NOTCH1, in five families. NOTCH1 is likely to be the major cause of AOS. NOTCH1 codes for a transcription factor that governs cell differentiation during embryonic development and throughout life.

BALIGA LAB

Sept. 18:
Uncovering the Genetic Adaptability of Tuberculosis

The Institute for Systems Biology and Seattle BioMed have collaborated to reconstruct the gene regulatory network of the human pathogen Mycobacterium tuberculosis. Finely tuned gene regulation has allowed Mycobacterium tuberculosis to survive unnoticed in an apparently healthy host for decades; understanding those subtleties is critical for advancing treatment. The identification of co-regulated sets of genes and their regulatory influences offers validated predictions that will help guide future research into Mycobacterium tuberculosis pathogenicity.

HOOD LAB

Sept. 22:
ISB Gets $2.3 Million NIH Grant to Use Single-Cell Technology to Fight Cancer

ISB has received a $2.3 million NIH grant over four years in response to NCI's "Provocative Questions" Initiative. The project will apply ISB's most advanced single-cell omics technologies to an innovative clinical trial for colorectal cancer (ADAPT). Principal investigator Qiang Tian, MD, PhD, head of the Cancer & Stem Cell Group, explained that the goal is to identify single cell signatures that can be used to stratify those patients who respond well to the treatment from those who are resistant to the treatment. For the patients who do not respond, the hope is to figure out a better treatment scheme from the study.

Headlines 2014
Continued

BALIGA LAB

Sept. 25:
New Tool Uses 3D Protein-DNA Structures to Predict Locations of Genetic 'On-Off' Switches

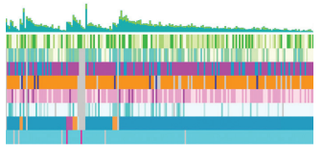
Novel systems approach uses high-resolution structures of protein-DNA complexes to predict where transcription factors (genetic switches) bind and regulate the genome. This approach can help researchers better understand and predict binding sites for non-model organisms or 'exotic' species. Having such insight and predictive capabilities is critical for reverse- and forward-engineering organisms that could be pivotal for new green biotechnologies.

SHMULEVICH LAB

Oct. 10:
ISB Awarded $6.5 Million NIH Contract to Develop 'Cancer Genomics Cloud' with Google and SRA International

ISB received a $6.5 million, up to two-year, federally funded contract from the National Cancer Institute (NCI), National Institutes of Health (NIH). ISB is one of three organizations awarded a contract by NCI to develop a cloud-based platform that will serve as a large-scale data repository and provide the computational infrastructure necessary to carry out cancer genomics research at unprecedented scales. ISB's Shmulevich group serves as the lead on the project with two partners: Google, Inc., and SRA International, Inc. (a Fairfax, Va.based provider of IT solutions and professional services to government organizations).

SHMULEVICH LAB



Oct. 23:
New Details on Thyroid Cancer May Lead to More Precise Therapies

Papillary thyroid cancer represents 80 percent of all thyroid cancer cases. Integrative analysis resulted in the detection of significant molecular alterations not previously reported in the disease. ISB researchers identified microRNAs which may lead to more precise therapy.

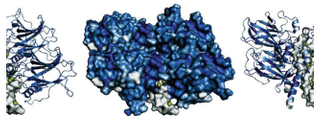
Headlines 2014
Continued

AITCHISON LAB

Oct. 28:
A New Approach to Identifying How the Deadly Dengue Virus Multiplies

Dengue virus is the most prevalent mosquito-borne virus worldwide, infecting an estimated 400 million people per year and causing about 25,000 deaths. It's necessary to understand the molecular mechanisms of dengue replication in order to develop an effective treatment. Researchers at ISB and Seattle BioMed developed a novel approach for identifying host proteins that associate with dengue replication machinery.

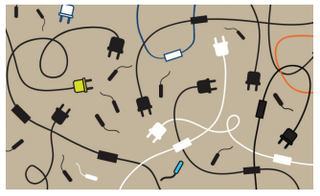
BALIGA LAB



Nov. 6:
How Physics and Thermodynamics Help Assess DNA Defects in Cancer

'Big data' cancer research has revealed a new spectrum of genetic mutations across tumors that need understanding. Existing methods for analyzing DNA defects in cancer are blind to how those mutations actually behave. ISB scientists developed a new approach using physics- and structure-based modeling to systematically assess the spectrum of mutations that arise in several gene regulatory proteins in cancer.

BALIGA LAB



Nov. 17:
How One Family of Microbial Genes Rewires Itself for New Niches

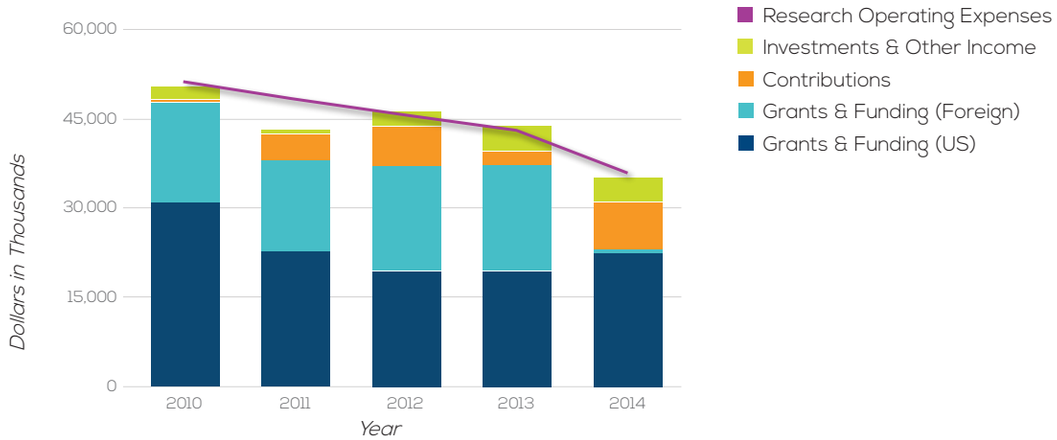
When an organism duplicates its genes, it increases its ability to adapt and colonize new environments. ISB researchers used the systems approach to study how one family of microbial genes evolved to bring functions that were adaptive to specific environments. This new understanding of how gene regulatory networks rewire themselves has many potential applications, including how to wire new functions into an organism for biofuel production, bio-remediation or bio-pharmaceutical production.

FINANCIALS

For the year ending December 31, 2014

5-YEAR OVERVIEW

Research Operating Expenses vs. Total Revenue



STATEMENT OF ACTIVITIES

Dollars in Thousands

Revenues	$	%
Grants & Contract Revenue	23,244	65.7
Contributions	7,896	22.3
Investments & Other Income	4,260	12.0
Total Revenues	**35,400**	**100.0**

Expenditures	$
Research & Other Direct Costs	24,322
Management & General	11,460
Fundraising & Other	188
Total Expenditures	**35,970**
Decrease in Net Assets	**(570)**

BALANCE SHEET

Dollars in Thousands

Assets	$
Cash & Investments	18,427
Other Assets	13,549
Property & Equipment (Net)	10,578
Total Assets	**42,554**

Liabilities	$
Accounts Payable & Accrued Expenses	14,825
Deferred Revenues	3,731
Notes Payable	7,782
Total Liabilities	**26,338**

Net Assets	$
Unrestricted Net Assets	(197)
Temporarily Restricted Net Assets	7,741
Permanently Restricted Net Assets	8,672
Total Net Assets	**16,216**

ABOUT ISB

The Institute for Systems Biology (ISB) is a nonprofit 501(c)(3) biomedical research organization based in Seattle, Washington. It was founded in 2000 by systems biologist Lee Hood, MD, PhD, immunologist Alan Aderem, PhD, and protein chemist Ruedi Aebersold, PhD.

ISB was established on the belief that the conventional models for exploring and funding breakthrough science have not caught up with the real potential of what is possible today.

ISB serves as the ultimate environment where scientific collaboration stretches across disciplines, where our researchers have the intellectual freedom to challenge the status quo, and where grand visions for breakthroughs in human health inspire a collective drive to achieve the seemingly impossible.

Our core values ensure that we maintain our focus on the big ideas that will have the biggest impact on human health.

ISB's annual operating budget is $35.7 million, which is supported by the NIH and other federal government agencies, global strategic partnerships, private philanthropy, and foundations.

ADDRESS

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ONLINE

systemsbiology.org